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Histology-based survival outcomes in breast cancer patients treated with CDK4/6 inhibitor

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Abstract

Aim: Metastatic breast cancer that is hormone receptor-positive and HER2-negative has shown significant advancements in the past decade with the introduction of CDK4/6 inhibitor therapies in the first-line treatment. The aim of our study is to compare the prognosis of CDK4/6 inhibitors combined with endocrine therapy in lobular breast cancer (LBC) and invasive breast carcinoma of no special type (IBC/NST) histologic subtypes.

Material and Methods: We included hormone receptor-positive HER2-negative metastatic breast cancer patients with known histological subtypes and survival times who were initiated on CDK4/6 inhibitor combined with endocrine therapy as first-line treatment.

Results: Out of the 248 patients included in the study, 13.3% (33) had the histologic subtype of lobular breast cancer. The median progression-free survival (mPFS) was 28 months (95% CI: 21.4-34.6) in IBC/NST patients and 31 months (95% CI: 21.2-40.8) in LBC patients (p = 0.861). The median overall survival was 81 months (95% CI: 43.3-118.8) in IBC/NST patients and 66 months (95% CI: 25.3-106.7) in LBC patients (p = 0.112). There were no significant differences in median progression-free survival and median overall survival times between the IBC/NST and LBC groups in both univariate and multivariate analyses.

Discussion: While IBC/NST and LBC have been recognized in the literature as distinct sub-histologic breast cancer groups with varying responses to specific drugs and disease progression, our study revealed that they exhibited similar survival outcomes with the use of CDK4/6 inhibitor therapies.

Keywords

CDK4/6 Inhibitor, Lobular Breast Carcinoma, Invasive Breast Carcinoma/No Special Type (IBC/NST), Histologic Subtypes

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Introduction

The treatment of hormone receptor-positive, HER2-negative metastatic breast cancer (HR+/HER2-mBC) has evolved over the past decade from using hormonal therapies alone to the combination of CDK4/6 inhibitors (CDK4/6i) and endocrine therapy (ET) [1]. The most important reason for this change is the discovery of new targets from studies on the mechanisms that cause hormone resistance [2]. Although treatment for these patients is now conducted according to guidelines with standard approaches and CDK4/6i and ET are used as the first-line standard treatment for HR+/HER2-mBC, numerous studies continue to explore which patients derive the greatest benefit from this treatment modality [3]. The basic molecular and histopathologic features associated with the disease gain particular importance.

Invasive breast cancer is a disease that is characterized by more than 20 histological subtypes. The most common subtype, accounting for approximately 80% of cases, is invasive ductal carcinoma (IDC), also classified as invasive carcinoma of no special type (IBC/NST) [4]. Invasive lobular carcinoma (ILC) constitutes approximately 10-15% of breast cancers and differs from IBC/NST in clinical, pathological, and molecular features [5]. One of the critical characteristics of ILC is the loss of the cell adhesion protein E-cadherin in approximately 90% of cases. ILC is typically associated with low grade, low proliferation index, and strong ER positivity [6]. However, compared to IBC/NST, ILC has been observed to have a higher risk of distant recurrence after ten years and exhibits distinct metastatic patterns [7]. ILC is also thought to show a weaker response to systemic chemotherapy than IBC/NST, and there is evidence from cell line studies suggesting a higher likelihood of resistance to tamoxifen in ILC [8].

The phase studies leading to the approval of CDK4/6i and ET combination therapy included patients with predominantly IBC/NST as a histologic subtype. Although the LBC histological subtype is available in phase studies, there is no data regarding the benefit of CDK4/6 combinations as a subgroup. Our study aimed to compare the real-life survival outcomes of CDK4/6i combinations in LBC and IBC/NST patients.

Material and Methods

Between January 2019 and January 2023, 248 HR+/HER2- mBC patients with known histological subtypes and survival times who were started on CDK4/6i treatment in a first-line setting at Dr. Abdurrahman Yurtaslan Ankara Oncology Hospital were included in the study.

The histologic subtyping of BC was performed by experienced pathologists who reviewed hematoxylin and eosin-stained sections of the tumor samples obtained from biopsy or surgical resection specimens. Invasive ductal carcinoma (IDC), commonly classified as invasive carcinoma of no special type (IBC/NST), is considered the subtype of breast cancer in this study, and patients with invasive lobular carcinoma (ILC) were also included. Less common histological subtypes were excluded from the study.

Our study included female patients between the ages of 18 and 80. Patients without histological subtype information and those who received CDK4/6i treatment after the first line were excluded from the study.

Statistical analyses were performed using SPSS version 22.0, and $p < 0.05$ was considered statistically significant. Descriptive analyses were performed for the demographic and clinical characteristics of the patients. Wilcoxon test was used to analyze repeated nonparametric measurements. The difference in continuous numerical variables between the two groups was evaluated with the Student's t-test. The Chi-square test describes the relationship between two separate categorical groups. Kaplan-Meier survival analysis method was used. Independent samples t-test was used for ordinal variables, and Cox regression analysis was used for categorical variables in univariate analysis. Cox regression analysis was also used for multivariate analysis.

Ethical Approval

This study was approved by the Ethics Committee of Dr. Abdurrahman Yurtaslan Ankara Oncology Hospital (Date: 2024-02-22, No: 2024-02/08).

Results

Of the 248 patients included in the study, 13.3% (n = 33) had LBC histologic subtype. The median follow-up period of the patients was 30(CI 95%:25-32) months. Patient-related variables according to histologic subtypes are given in Table 1. The mean age in the whole group was 56.6 ± 12.6 years. The mean age of LBC patients was 56.8 ± 10.3 years, while that of IBC/NST patients was 56.6 ± 12.9 years (p = 0.921). ECOG performance score, presence of comorbidities, menopausal

Table 1. Demographic and clinical characteristics of the patients

Variables	Total	LBC	IBC/NST	P
Age (mean±std)	100(248)	13.3(33)	86.7(215)	0.921
	56.6±12.6	56.8±10.3	56.6±12.9	
ECOG (%n)				
0-1	92.7(230)	97(32)	92.1(198)	0.315
>1	7.3(18)	3(1)	7.9(17)	
Comorbidity(%n)				
Yes	54(134)	54.5(18)	54(116)	0.949
No	46(114)	45.5(15)	46(99)	
Menopausal status (%n)				
Post-menopausal	69.8(173)	72.7(24)	69.3(149)	0.690
Pre-menopausal	30.2(75)	27.3(9)	30.7(66)	
Metastatic status(%n)				
De-novo	49.2(122)	57.6(19)	47.9(103)	0.301
Recurren	50.8(126)	42.4(14)	52.1(112)	
Metastatic site(%n)				
Non-visceral	62.9(156)	60.6(20)	63.3(136)	0.769
Visceral	37.1(92)	39.4(13)	36.7(79)	
CDK4/6 Treatment option (%n)				
Ribociclib	70.6(175)	63.6(21)	71.6(154)	0.348
Palbociclib	29.4(73)	36.4(12)	28.4(61)	
CDK4/6 combination(%n)				
AI	77.8(193)	72.7(24)	78.6(169)	0.449
Fluvestrant	22.2(55)	27.3(9)	21.4(46)	

*significant
**LBC=Lobular breast carcinoma
*** IBC/NST=Invasive ductal carcinoma – no special type

status, disease status at diagnosis, site of metastasis, CDK4/6i type, and hormonal therapy type were similar between LBC and IBC/NST patients(p = 0.315, p = 0.949, p = 0.690, p = 0.301, p = 0.769, p = 0.348, p = 0.449, respectively).

When the factors that may affect survival were evaluated by univariate analysis, age, presence of comorbidities, menopausal status, disease status at diagnosis, site of metastasis, CDK4/6i type and hormonal therapy type and histological subtype did not affect PFS(p=0.395, p = 961,p = 287, p = 0.055, p = 0,204, p = 0.730, p = 0.078, p = 0.863, respectively) (Table 2). However, ECOG performance status affected PFS (p < 0.001) (Table 2).

When all variables in the univariate analysis were included in the multivariate analysis, the ECOG performance score remained significant, and disease status at diagnosis became significant.

Table 2. Univariate and multivariate analyses to estimate PFS

Variables	Univariate analyses			Multivariate analyses		
	HR	CI 95%	P value	HR	CI 95%	P value
Age	0.99	0.98-1.01	0.395	0.98	0.96-1.01	0.162
ECOG						
0-1	3.29	1.87-5.81	<0.001*	4.36	2.29-8.31	<0.001*
>1						
Comorbidity						
Yes	0.99	0.68-1.44	0.961	0.91	0.60-1.37	0.648
No						
Menopausal status						
Post-menopausal	1.24	0.83-1.85	0.287	1.5	0.57-1.91	0.882
Pre-menopausal						
Metastatic status						
De-novo	1.45	0.99-2.11	0.055	1.54	1.00-2.37	0.050*
Recurren						
Metastatic site						
Non-visceral	1.28	0.87-1.88	0.204	1.21	0.81-1.92	0.324
Visceral						
CDK4/6 Treatment option						
Ribociclib	1.7	0.71-1.60	0.730	1.4	0.68-1.58	0.867
Palbociclib						
CDK4/6 combination						
AI	1.49	0.96-2.32	0.078	1.25	0.76-2.07	0.378
Fluvestrant						
Histology						
LBC	0.95	0.54-1.67	0.863	1.5	0.59-1.87	0.856
IBC/NST						

*significant
**LBC=Lobular carcinoma
*** IBC/NST=Invasive ductal carcinoma – no special type

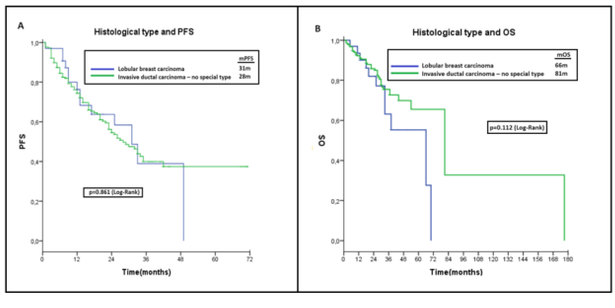

Figure 1. Survival analysis

However, the histological subtype did not affect PFS (p < 0.001, p = 0.050, p = 0.856, respectively).

Median PFS was 28 months (95% CI: 21.4-34.6) in IBC/ NST patients and 31 months (95% CI 21.2-40.8) in LBC patients (p = 0.861) (Figure-1). Median OS was 81 months (95% CI: 43.3-118.8) in IBC/ NST patients and 66 months (95% CI: 25.3-106.7) in LBC patients (p = 0.112) (Figure-1).

Discussion

In the context of ILC, the benefit of CDK4/6is has been studied less than that of IDC. However, a pooled analysis of phase studies reported by the U.S. Food and Drug Administration (FDA) indicated that both IDC and ILC patients benefited from the addition of a CDK4/6i to aromatase inhibitor (AI) therapy in terms of PFS [9]. This suggests that CDK4/6i may also be beneficial for ILC patients. Similarly, an updated analysis showed that both IDC and ILC patients experienced a longer OS duration by adding a CDK4/6i to AI [10]. These findings suggest that CDK4/6is may positively impact the outcomes of ILC patients, similar to their effects in IDC patients. Although these pooled analyses shed light on the potential impact of CDK4/6i in ILC, real-life data, and further research specifically focusing on ILC are needed to understand better these agents' efficacy and safety profile in this patient population.

In the study conducted in 2022 from MD Anderson BC databases, they did not find a statistically significant difference in PFS and OS duration between IDC and ILC patients receiving CDK4/6i and ET without or with stratification according to first-line or second-line treatment and above [11]. This analysis was the first known retrospective real-life data with a large number of patients, and the results were similar to our study. However, unlike our study, there were very few ribociclib patients (5/336) and predominantly palbociclib (310/336) patients in this study. In our study, predominantly patients receiving ribociclib, there was no significant difference in the number of patients receiving ribociclib and palbociclib between the ILC and IBC/NST groups, and in univariate analyses, PFS and OS were similar in both subgroups regardless of the treatment option. Therefore, our study emphasizes the real-life efficacy of ribociclib in the ILC subgroup.

In the MD Anderson BC database study [11], mPFS duration was 16.0 months for IDC compared to 18.8 months for ILC (HR, 1.04; 95% CI, 0.84-1.30; P = 0.675) even in patients receiving CDK4/6i and ET in the first line, which was found to be shorter compared to the analyses of the PALOMA-2, MONALEESA-2, and MONALEESA-7 trials [12]. In our study, mPFS was 28 months (95% CI: 21.4-34.6) in IBC/NST patients and 31 months (95% CI: 21.2-40.8) in LBC patients, consistent with the literature data. Since it increases the reliability of the data used in the analysis, it significantly determines survival times similar to those in the literature.

In 2022, a study presented at the 13th European Breast Cancer Conference evaluated 33 patients with LBC or mixed histology. Among these, 18 received CDK4/6 inhibitors as first-line treatment. The median follow-up time was 12.5 months, and the median mPFS was reported as 13.2 months, with the median value not reached. The study was published as single-center data from Portuguese [13]. Also provides insight into a

heterogeneous group of LBC patients in which 13/30 (43%) patients received Palbociclib, 14/30 (47%) Ribociclib, and 3/30 (10%) Abemaciclib, published as an abstract in Annals of Oncology in 2023 [14]. Our study stands out from these studies by being conducted on a more homogeneous group, including a larger patient cohort, and showing survival outcomes that align with existing literature. Furthermore, it contributes to the literature by comparing IBC/NST and LBC.

The limitation of our study is the low number of LBCs since they constitute only 10-15% of all breast cancers. Other significant limitations include the lack of knowledge of the treatments received after the first line and the retrospective design. In our study, the primary reason for the discordance between OS and PFS durations has been considered to be the small number of ILC patients and the lack of knowledge regarding the management of second-line treatments.

In conclusion, although studies have shown that IBC/NST and LBC differ in treatment responses with some drugs and clinical progression patterns, mPFS and mOS times are similar with first-line CDK4/6i and ET treatment. The number and scope of studies comparing the response of breast cancer sub-histological types to CDK4/6i are limited. Thus, our study contributes to the literature.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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